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Nutritional status, the development and persistence of malnutrition and dietary intake in oesophago-gastric cancer: a longitudinal cohort study

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The authors have nothing to declare.

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Transparency Declaration Statement

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Abbreviations: ANOVA, analysis of variance; FFQ, food frequency questionnaire; GI, gastrointestinal ; GSRS, Gastrointestinal Symptom Rating Scale; OG, oesophago-gastric; PG-SGA, Patient-Generated Subjective Global Assessment

ABSTRACT

Background:

Patients with oesophago-gastric (OG) cancer may be at risk of malnutrition, troublesome gastrointestinal symptoms (GI) and reduced dietary intake in view of the tumour location and multimodality curative treatment approach. Longitudinal research is lacking. This study aimed to assess (1) nutritional status and how it evolved over the first year, (2) the association between nutritional status scores and GI symptom scores and (3) the nutrient and food group intake pattern.

Methods:

This was a prospective, observation study of patients with an OG lesion planned for radical treatment, with assessment at diagnosis, 3-months and 12-months following the start of treatment. Nutritional assessment was performed using the Patient-Generated Subjective Global Assessment (PG-SGA), GI symptoms measured using the modified Gastrointestinal Symptom Rating Scale and dietary intake assessed using a semi-quantitative food frequency approach.

Results:

80 patients (61 males, 19 females; aged 46-89y) were recruited. At baseline, 3 (n= 68) and 12 months (n= 57), 61%, 62% and 60% respectively were moderately/severely malnourished. Higher symptom burden was associated with poorer nutritional status at baseline ($r= +0.55$, $p< 0.001$), 3-months ($r= +0.51$, $p< 0.001$) and at 12-months ($r= +0.42$, $p= 0.001$). At each respective time point, 37%, 38% and 42% were meeting their Estimated Average Requirement for energy. No change in mean (SD) intake of energy, fibre, nutrient and food groups over time were observed.

Conclusion:

Patients with OG cancer have progressive weight loss, with malnutrition present in the majority during this year. Optimising nutritional status and symptom management throughout the treatment pathway should be a clinical priority.

Keywords: Undernutrition, nutritional status, gastrointestinal, gastric, oesophageal, cancer

INTRODUCTION

Disease-related malnutrition occurs frequently in patients with cancer, with a high incidence in patients with oesophago-gastric (OG) cancer, ranging from 37-63% (1-3). The prevalence is dependent on tumour type and location, disease staging, treatment received and type of nutritional assessment method used (4,5). Most prevalence data is cross-sectional, not accounting for variations in nutritional status and malnutrition at different stages of treatment. The consequences of malnutrition in cancer are well recognised and include important adverse effects on clinical outcome e.g. increased risk of morbidity, decreased response and tolerance to treatment, decreased performance status and lower quality of life (6-10).

It is likely that malnutrition and nutritional deterioration in OG cancer are caused by a dual mechanism, whereby negative local and systemic effects of the disease are compounded by acute and chronic nutrition-impact symptoms produced by treatments. Such treatment involves combinations of chemotherapeutic, radiotherapeutic and surgical regimens. A high burden of gastrointestinal (GI)

symptoms is observed, although their co-occurrence and potential causal connection with malnutrition remains unclear (11-13). Likewise, inadequate oral intake may contribute to malnutrition in OG cancer but there are few studies assessing dietary intake, and those that do are very heterogeneous, use different dietary assessment methods and present conflicting results (14-16). Therefore, the contribution of inadequate oral intake to malnutrition in patients with OG cancer is uncertain.

To date, the nutritional status, GI symptom burden or dietary intake of OG cancer patients has not been systematically measured longitudinally. This study aimed to (1) assess nutritional status and the prevalence of malnutrition at diagnosis and in the early (3 months, 3 m) and later stages (12 months, 12 m) of treatment; (2) determine the association between GI symptom scores and nutritional status and malnutrition; and (3) assess nutrient and food group intake and its association with nutritional status and malnutrition.

METHODS

Subjects and Study Design

A prospective, longitudinal cohort study of patients with a new oesophageal, gastro-oesophageal or gastric cancer (or pre-malignant disease of these locations) was conducted at a tertiary cancer centre in the United Kingdom, The Royal Marsden NHS Foundation Trust. Eligibility criteria were: cancer/pre-malignant disease confirmed by histopathology; planned to undergo radical treatment. Exclusion criteria were: age <18 years; receiving private healthcare; previous OG cancer; oncological treatment started >1 week before consent; unable to give informed consent.

Each patient with a new OG cancer diagnosis was discussed at a weekly OG specialist multi-disciplinary team meeting at the tertiary cancer centre. Here, a treatment plan was established for each individual and the study's registered dietitian screened patients to identify those fulfilling the study's inclusion criteria. Given the vulnerability of the patient group, the study dietitian liaised with other members of the multi-disciplinary team to determine the most appropriate time for her to approach eligible patients. This was often at one of their routine out-patient appointments with their oncologist or surgeon.

Patients gave informed consent before study enrolment, with recruitment from 18th November 2011 - 17th May 2013. The study visits were at diagnosis (before starting treatment) and at 3 m and 12 m after the treatment start date. Measurements of nutritional status, GI symptoms and dietary intake were taken by the same study dietitian at each time point.

The study was reviewed and approved by the institutional clinical research and local ethics committees. The procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Nutritional Status

Weights and heights were measured by the study dietitian using the Marsden M-120 Column Scales and the Marsden HM-200 Telescopic Height Measure respectively. The equipment was serviced and calibrated every six months by the equipment manufacturer. When measuring weight, the scales was positioned on a level surface, the patient removed their shoes and wore light day clothing (items in pockets and jewelry were removed). The presence of ascites and/or oedema was noted and where present, an estimated weight was recorded.

Nutritional assessment was undertaken using the Patient Generated Subjective Global Assessment (PG-SGA) (17). It is the only validated and specific tool for a thorough nutritional assessment in oncology and has been accepted as the standard for nutrition assessment in oncology.

The PG-SGA has two sections: a patient-completed component and a clinician component. The former has four parts (weight loss, nutrition impact symptoms, nutritional intake and functional capacity). The later also has four parts, which produces scores for diagnosis, age, metabolic stress, with a subjective physical examination assessing fat, muscle stores and fluid status. Finally, a global assessment of nutritional status is produced.

The PG-SGA produces both subjective global ratings and a PG-SGA total score. The subjective global rating categories are consistent with the three categories from the Subjective Global Assessment (SGA) tool: PG-SGA-A (well-nourished), PG-SGA-B (moderately/suspected malnourished) and PG-SGA-C (severely malnourished). PG-SGA total scores range from 0-49, with triage recommendations as follows: score 0-1 (no intervention required); score 2-3 (patient and family education with pharmacological intervention and/or laboratory values); score 4-8 (requires intervention by dietitian in conjunction with nurse or physician); score ≥ 9 (critical need for improved symptom management and/or nutrient intervention options).

For ethical reasons standard clinical practice was followed regarding dietary intervention in study patients. That is, members of the multidisciplinary team were able to refer patients to a separate

clinical dietitian based upon their own clinical opinion. The study dietitian would also refer patients to the clinical dietitian in those with a PG-SGA total score of ≥ 4 .

Gastrointestinal Symptoms

Presence and severity of GI symptoms were measured using a modified version of the original 15-symptom Gastrointestinal Symptom Rating Scale (GSRS) (18). The purpose of modification, was to increase the time over which the tool captures symptoms and to make it more disease-specific by adding relevant symptoms (dysphagia to fluids and/or solids, odynophagia to fluids and/or solids, early satiety, regurgitation of fluids and/or solids, faecal incontinence) and by removing symptoms considered irrelevant (hunger pains and sucking sensation in epigastrium). The modified tool measured 22 GI symptoms over the previous four weeks using a 4-point Likert scale (0= absent symptom; 1= mild symptom occurring occasionally but did not impact much; 2= moderate symptom occurring often and that impacted quite a bit; 3= severe symptom occurring a lot and that impacted a great deal). Individual scores were recorded for each GI symptom, and the sum of all 22 GI symptom scores was used to produce a GSRS total score (potential minimum score of 0 and maximum of 66).

Dietary Intake

The dietary assessment tool was the European Prospective Investigation into Cancer Food Frequency Questionnaire (FFQ) (Norfolk version). This is a semi-quantitative FFQ validated for assessing habitual dietary intake for the previous 12 months in the European Prospective Investigation into Cancer population (19-22). This FFQ contains a list of 130 foods items and a multiple response grid. Food lists and portion sizes are representative of an adult population in the United Kingdom following a traditional diet. Patients were requested to complete the FFQ based upon intake over the previous one month (rather than over the previous 12 months) so as to align with the study design.

Data entry and analysis of the FFQs was undertaken using FETA software to produce nutrient and food group intake data (23). Data on intake of vitamin and micronutrient supplements, oral nutritional supplements and enteral nutrition were collected but could not be computed using FETA software. The data presented are for oral intake from food exclusively.

Statistical Analysis

As this was an observational study, with no group comparisons and no reporting of effect size, it was not necessary to power the study. A maximum recruitment period of 18 months was possible. No missing data was replaced. Statistical analyses were conducted using the Statistical Package for the Social Sciences software (version 22.0, IBM, USA). Paired continuous data were compared using

paired t-tests, with a 2-sided significance level of 5% used to assess significant difference between the data. The Kolmogorov-Smirnov test was used to examine the distribution of GSRS total scores and PG-SGA total scores, both of which were non-normally distributed. Median and range were used to summarise the data and the data were compared between different time points using non-parametric tests (Wilcoxon test). All other data were normally distributed.

Change in patients' PG-SGA category between baseline and 3 m and between baseline and 12 m were undertaken using cross-tabulation.

The association between GI symptoms and nutritional status was measured in three ways. The association between overall GI symptoms (GSRS total scores) and nutritional status (PG-SGA total scores) were analysed using a Spearman's rank correlation. Data were visualised using scatter plots and Dancey and Reidy's categorisations aided the determination of the strength of the correlation using correlation co-efficients (r) (24). The nutritional status (PG-SGA total scores) of patients with (mild/moderate/severe) and without (absence) each of the GI symptoms was compared using a chi-square test. Finally, a cross-tabulation was performed to compare those with presence (i.e. mild, moderate or severe) and absence of each GI symptom measured with respect to malnutrition category (PG-SGA A and PG-SGA B+C).

Descriptive analysis was undertaken to report the FFQ data using mean (SD) intake of energy, macronutrients, micronutrients and fibre and 14 food groups. For those with three FFQs, repeated measures analysis of variance (ANOVA) compared the intakes at the three time points, and where $p < 0.05$, a Bonferroni post-hoc test was performed to determine the differences between each time point. The proportion meeting their requirements at each study visit was calculated by comparison with the relevant Dietary Reference Value for energy (Estimated Average Requirement) and protein (25).

RESULTS

The participant flow chart is shown in the Figure contained in the supplementary material: 80 patients were recruited; 68 completed the 3 m assessment; 57 completed the 12 m assessment. The baseline characteristics and treatment details of the 61 (76%) males and 19 (24%) females are shown in **Table 1**. A number of patients had at least one consultation with a clinical dietitian as either an in- or out-patient in the three-month period before baseline (32, 40%), in the baseline to 3 m period (45, 66.2%) and in the 3 m to 12 m period (42, 73.7%). The mean (SD) number of consultations with the clinical dietitian per patient, for the respective periods was 1.6 (0.9), 3.2 (4.3) and 7.9 (7.4).

245 **Nutritional Status**

246 The mean (SD) body weights at baseline (n= 80), 3 m (n= 68) and 12 m (n= 57) were: 76.6 (17.2) kg,
 247 74.4 (14.8) kg and 71.6 (16.7) kg respectively, with BMIs of 26.7 (4.7) kg/m², 25.9 (4.1) kg/m² and
 248 25.0 (4.9) kg/m² respectively. Paired score comparisons were performed for those with data available
 249 at two (or more) time points, with significant reductions in weight and BMI as per the p-values: for
 250 baseline to 3 m they were 0.003 and 0.006 respectively; for baseline to 12 m and also for 3 m to 12
 251 m they were < 0.001 and < 0.001 respectively. Of the patients with all data points, n= 12 (21%) gained
 252 weight from baseline to 12 m, with a mean percentage weight gain of 6.1%. The remaining n= 45
 253 (79%) lost weight, with a mean percentage weight loss of 11.1% over the 12 m period.

254
 255 The scores from the components of PG-SGA are reported in **Table A of the supplementary material**.
 256 The proportion experiencing recent unintentional weight loss decreased from 57.5% at baseline to
 257 42.7% at 3 m and 26.3% at 12 m. For worksheet 4 (nutrition-related physical examination and
 258 anthropometric assessment), at least 30% of patients were found to have some depletion of fat and
 259 muscle stores (and/or the presence of ascites/oedema). The prevalence of moderate/suspected/severe
 260 malnutrition was 61.2% at baseline, 61.8% at 3 m and 59.6% at 12 m (**Table 2**). No significant
 261 difference in PG-SGA score between any time points was identified.

262
 263 Using the cross-tabulation method, it was noted that from baseline to 12 m (n= 57), 14 (24.6%)
 264 improved their nutritional status category, 16 (28%) worsened their category and 27 (47.4%)
 265 remained stable. Nineteen (33%) patients were moderately/severely malnourished at both diagnosis
 266 and 12 m (i.e. malnutrition 'persisted'), while 15 (27%) were well-nourished at diagnosis but became
 267 moderately/severely malnourished by 12 m (i.e. malnutrition 'developed').

269 **Association Between Gastrointestinal Symptoms and Nutritional Status**

270 The median (range) GSRS total score at baseline (n= 80) was 12/66 (0-46), at 3 m (n= 68) was 9.5/66
 271 (0-39) and at 12 m (n= 57) was 12/66 (0-46). There was moderate correlation between GSRS total
 272 score and PG-SGA total score at baseline (r= +0.55, p< 0.001), 3 m (r= +0.51, p< 0.001) and 12 m
 273 (r= +0.42, p= 0.001). At baseline, there was a greater prevalence of moderate/severe malnutrition in
 274 patients with 11 individual GI symptoms (dysphagia to solids, dysphagia to fluids, odynophagia to
 275 solids, odynophagia to fluids, belching, nausea, early satiety, abdominal grumbling, hard stools,
 276 constipation, incomplete evacuation), at 3 m there was a greater prevalence for only three GI
 277 symptoms (early satiety, constipation, incomplete evacuation). There were no significant differences
 278 in prevalence of malnutrition between those with and without GI symptoms at 12 m (**Table 3**)

279

Dietary Intake

At baseline, 3- and 12 m, 79/80 (98.8%), 62/68 (91.2%) and 53/57 (92.9%) were managing some oral intake respectively, with 18 (22.5%), 13 (20.9%) and 5 (9.4%) consuming foods with a modified texture. Of these, 3.8% at baseline, 58.1% at 3 m and 5.7% at 12 m had an oesophageal stent; while 25.3%, 38.2% and 28.1% were prescribed oral nutritional supplements. There were 3/80 (3.8%), 7/68 (10.2%), 6/57 (10.5%) enterally fed (either sole or supplementary nutrition source) at baseline, 3 m and 12 m, with only 1/68 (1.5%) at 3 m requiring parenteral nutrition support.

78 FFQs were analysed at baseline, 61 at 3 m and 53 at 12 m. Of these patients, there were only 29 (37.2%) at baseline, 23 (37.7%) at 3 m and 22 (41.5%) at 12 m meeting their Estimated Average Requirement for energy from food, though more were achieving their Dietary Reference Value for protein at baseline (62, 79.5%), 3 m (54, 88.5%) and 12 m (48, 90.6%). 43 patients completed a FFQ at all three visits and the mean energy and protein intake per kg/day were as follows: 29.9 kcal/kg and 1.3 g/kg at baseline; 30.5 kcal/kg and 1.2g/kg at 3 m; 31.9 kcal/kg and 1.3g/kg at 12 m. Results for the comparison of daily energy, fibre, nutrient and food group intakes at each visit are shown in Table B of supplementary material. There was no significant change in the intake of any of the variables over time following Bonferroni post-hoc testing, where relevant.

DISCUSSION

This is the first study to record systematically nutritional status using a validated assessment method in OG cancer during the first year following diagnosis. Cancers of the GI tract are known to exert higher nutritional risk than other cancer sites (1,3,26). Heburterne et al.'s prevalence study indicated that patients with OG cancer had the second highest prevalence of malnutrition (60%) after pancreatic cancer. This supports earlier work where 61% of newly diagnosed OG cancer patients were shown to have > 5% unintentional weight loss (1). In the current study the prevalence of malnutrition was found to be 61% at baseline, and this value remained unchanged over time.

Although the overall values for malnutrition prevalence remained stable, this reflects a dynamic process of improvement, deterioration, and maintenance in different patients. Of those who were malnourished at baseline, this persisted until 12 m in one third, whilst of those who were well-nourished at baseline, one quarter developed malnutrition by 12 m, meaning that malnutrition persisted or developed in the majority.

While, we were already aware that gastrointestinal (GI) symptoms are observed in OG cancer patients (11-13), until now, we were unclear about their co-occurrence with malnutrition. Our results demonstrate moderate correlation between symptom and nutritional status scores throughout this first year. Importantly, we now have specific GI symptoms (in particular dysphagia, odynophagia, nausea, abdominal pain and early satiety) that we know to be associated with poorer nutritional status (Table 3). We know that by 12 m, most study patients no longer had cancer, so we suspect that their poor nutritional status had less to do with the primary effect of the cancer (i.e. imbalance between pro- and anti-inflammatory cytokines and abnormalities in substrate metabolism) and more to do with GI symptom burden.

Our study provides strength to the argument that the multidisciplinary approach towards treatment decisions should also be expanded to include much more active assessment and management of acute and chronic GI symptoms, to prevent them from negatively affecting nutritional status (27).

Likewise, inadequate oral intake may contribute to malnutrition in OG cancer but there are few studies assessing dietary intake in these patients. As per the 2017 ESPEN guidelines on nutrition in cancer patients, 25-30 kcal/kg/day and 1.2-1.5 g protein/kg/day can serve as a target ranges to help maintain or restore lean body mass, where individual measurements are unavailable (28). Results from this study suggest that inadequate oral intake is, indeed, likely to be playing a role in their malnutrition.

Although mean energy intake appeared adequate (30-32kcal/kg/day) to meet the ESPEN target, we note that less than half were meeting their Estimated Average Requirement for energy from food during the year. Similarly, while 80-90% were meeting their Dietary Reference Value for protein, with intakes of 1.2-1.3g/kg/day, ESPEN suggest that protein intakes should, if possible, reach 1.5 g/kg/day, especially where muscle depletion is present, as was the case in one-third of this cohort.

Considering these findings, and given that there was no increase in energy or protein intakes during the course of the study, we suggest that the chronic energy and protein deficits contributed, at least in part, to the ongoing weight loss observed. These data are concerning, considering that, following the commencement of treatment, the majority had at least one consultation with a clinical dietitian and many were taking oral nutritional supplements. This questions the effectiveness of current interventions (predominately food fortification advice and oral nutritional supplementation), and suggests that earlier and more intensive input (i.e. enteral support) may be necessary to prevent nutritional decline.

Best practice guidelines advocate for early identification and commencement of nutrition intervention to maintain quality of life (1,29,30). Also, the nutritional benefits of an early and intensive intervention (weekly dietetic consultations for 18 weeks) in OG cancer was demonstrated in a pilot study (31), with weight 6 kg greater and PG-SGA score 10 points lower in the intervention group compared with standard care group. Larger, well-conducted RCTs are required to better understand the effectiveness of intensive interventions.

Strengths and limitations

The decision to include patients with Barrett's oesophagus or a pre-malignancy may represent a limitation of this study considering these patients do not usually have dysphagia or weight loss at presentation. However, this should not materially affect the results as these patients were so few (n=4). Also of note, the groups of patients were not evenly distributed, as the majority were men. Many of the assessment methods relied, to varying extents, on recall, and therefore may be prone to recall bias.

Another weakness relates to the FFQ, which significantly overestimates energy and fibre intake, as well as many macro- and micronutrients when compared with weighed records (19). This means that caution should be used in applying the estimates of individual diets. In addition, the Dietary Reference Values provide a guide to the adequacy of dietary intake among healthy populations and therefore do not necessarily reflect the requirements of patients with cancer (32). Therefore, interpretation of the FFQ data must be done with caution.

This study's strength lies in its longitudinal design, which is atypical in cancer research concerned with nutrition, as the majority of data comes from cross-sectional studies. By following the course of nutritional status, dietary intake and GI symptoms over one year, these results highlight the importance of the comprehensive assessment from diagnosis, acutely during treatment and chronically. Attrition due to the death is inevitable in the context of longitudinal research in cancer patients and accounted for 18%. But the withdrawal and loss to follow-up rate was low at 11%. Neither inter-investigator bias nor non-random sampling are relevant here as one researcher completed all assessment and the recruited and declined populations were comparable (data not presented).

In conclusion, those with OG cancer experience a progressive weight loss over time and malnutrition is present in the majority during the first year. Current detection and treatment processes appearing sub-optimal. Optimising nutritional status throughout the treatment pathway should be considered a

384 priority in this high-risk group. We suggest an intensive approach, which might include weekly
385 nutritional assessment during oncological treatments, and follow-up after their completion until no
386 further risk exists. Ongoing assessment of GI function can be incorporated into the dietitian's
387 assessments, as well as other relevant health care providers. As this work has demonstrated that
388 symptom burden showed an association with nutritional status, whereby the presence of symptoms
389 tended to be associated with poorer nutritional status and *vice versa*, it seems reasonable to
390 hypothesize that the effective treatment of GI symptoms that are negatively impacting on dietary
391 intake would improve nutritional status.

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References

1. Baldwin C, McGough C, Norman AR, Frost GS, Cunningham DC, Andreyev HJN. Failure of dietetic referral in patients with gastrointestinal cancer and weight loss. *Eur J Cancer* 2006;42:2504–9.
2. Bozzetti F, Mariani L, Vullo LoS, SCRINIO Working Group, Amerio ML, Biffi R et al. The nutritional risk in oncology: a study of 1,453 cancer outpatients. *Support Care Cancer* 2012;20:1919–28.
3. Hebuterne X, Lemarie E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN* 2014;38:196–204.
4. Shike M. Nutrition therapy for the cancer patient. *Hematol Oncol Clin of North Am* 1996;10:221–34.
5. Martin L, Lagergren J, Lindblad M, Rouvelas I, Lagergren P. Malnutrition after oesophageal cancer surgery in Sweden. *Br J Surg* 2007;94:1496–500.
6. Ottery FDF. Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* 1996;12:S15–9.
7. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer* 1998;34:503–9.
8. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am J Med* 1980;69:491–7.
9. van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. *Eur J Oncol Nurs* 2005;9 Suppl 2:S51–63.
10. Kyle UG, Pirlich M, Lochs H, Schuetz T, Pichard C. Increased length of hospital stay in underweight and overweight patients at hospital admission: a controlled population study. *Clin Nutr* 2005;24:133–42.
11. Sánchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D.

- Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. *Br J Nutr* 2012;109:894–7.
12. Bovio G, Montagna G, Bariani C, Baiardi P. Upper gastrointestinal symptoms in patients with advanced cancer: relationship to nutritional and performance status. *Support Care Cancer* 2009;17:1317–24.
 13. Khalid U, Spiro A, Baldwin C, Sharma B, McGough C, Norman AR et al. Symptoms and weight loss in patients with gastrointestinal and lung cancer at presentation. *Support Care Cancer* 2007;15:39–46.
 14. Bae JM, Park JW, Yang HK, Kim JP. Nutritional status of gastric cancer patients after total gastrectomy. *World J Surg* 1998;22:254–60.
 15. Ludwig DJ, Thirlby RC, Low DE. A prospective evaluation of dietary status and symptoms after near-total esophagectomy without gastric emptying procedure. *Am J Surg* 2001;181:454–8.
 16. Carey S, Storey D, Biankin AV, Martin D, Young J, Allman-Farinelli M. Long term nutritional status and quality of life following major upper gastrointestinal surgery - A cross-sectional study. *Clin Nutr* 2011;30:774–9.
 17. Ottery FD. Nutrition Screening and Assessment in Oncology. In: McCallum P, Polisena C, eds. *The clinical guide to oncology nutrition*. Chicago: American Dietetic Association, 2000 11–23.
 18. Svedlund J, Sjödin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988;33:129–34.
 19. Bingham S. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol* 1997;26:S137–51.
 20. McKeown NM, Day NE, Welch AA, Runswick SA, Luben RN, Mulligan AA et al. Use of biological markers to validate self-reported dietary intake in a random sample of the European Prospective Investigation into Cancer United

- Kingdom Norfolk cohort. *Am J Nutr* 2001;74:188–96.
21. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51–65.
 22. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH et al. The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol* 1988;127:188–99.
 23. Mulligan AA, Luben RN, Bhaniani A, Parry-Smith DJ, O'Connor L, Khawaja AP et al. A new tool for converting food frequency questionnaire data into nutrient and food group values: FETA research methods and availability. *BMJ* 2014;4:1–12.
 24. Dancey CP, Reidy J. Chapter 5. In: Dancey CP, Reidy J, eds. *Statistics Without Maths for Psychology: using SPSS for Windows*. 3rd ed. Essex: Pearson Education, 2004 163-205.
 25. Scientific Advisory Committee on Nutrition. *Dietary Reference Values for Energy*. London: Stationery Office/TSO, 2012.
 26. Koom WS, Ahn SD, Song SY, Lee CG, Moon SH, Chie EK et al. Nutritional status of patients treated with radiotherapy as determined by subjective global assessment. *Radiat Oncol J* 2012;30:132.
 27. Grover S, Lim RM, Blumberg RS, Syngal S. *Oncogastroenterology*. *J Clin Oncol* 2016;34:1154–5.
 28. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36:11–48.
 29. Bauer JD, Capra S. Nutrition intervention improves outcomes in patients with cancer cachexia receiving chemotherapy? A pilot study. *Support Care Cancer* 2005;13:270–4.
 30. Ottery FD. Cancer cachexia: prevention, early diagnosis, and management.

Cancer Pract 1994;2:123–31.

31. Silvers MA, Savva J, Huggins CE, Truby H, Haines T. Potential benefits of early nutritional intervention in adults with upper gastrointestinal cancer: a pilot randomised trial. Support Care Cancer 2014;22:3035–44.
32. Committee on Medical Aspects of Food Policy (Department of Health, ed). Dietary Reference for Food Energy and Nutrients for the United Kingdom. London: Stationery Office/TSO, 1991.

Table 1: Baseline characteristics and treatment details of the recruited cohort¹

Baseline characteristics	Males (n= 61)	Females (n= 19)
Age (y), median (min-max)	66 (47-89)	61 (46-80)
Eastern Cooperative Oncology Group performance status		
0	25 (41)	10 (52.6)
1	31 (50.8)	8 (42.1)
2	4 (6.6)	1 (5.3)
3	1 (1.6)	0 (0)
4	0 (0)	0 (0)
Current diagnosis		
AC of upper and middle third of oesophagus	21 (34.4)	2 (10.5)
AC of lower third of oesophagus, Siewert type I	12 (19.7)	2 (10.5)
SCC of the oesophagus	8 (13.1)	4 (21.1)
Siewert type II and III	3 (4.9)	3 (15.8)
AC of stomach	11 (18)	4 (21.1)
Gastrointestinal stromal tumour of the stomach	2 (3.3)	3 (15.8)
Barrett's oesophagus	1 (1.6)	0 (0)
Other malignant/premalignant neoplasm	3 (4.9)	1 (5.3)
Histopathological tumour (T) staging		
0-1	5 (8.2)	1 (5.3)
2	9 (14.8)	5 (26.3)
3	41 (67.2)	7 (36.8)
4	4 (6.6)	1 (5.3)
Not applicable	2 (3.2)	5 (26.3)
Undergoing active oncological treatment		
At 3 m (n= 68)		
At 12 m (n= 57)		
Treatment modalities received up to 12 m (n= 57)		
Surgery alone 3 (5.3)		
Surgery and chemotherapy 32 (56.1)		
Surgery, chemotherapy and radiotherapy 7 (12.3)		
Chemotherapy and radiotherapy 13 (22.8)		

Chemotherapy alone 2 (3.5)

¹All values are expressed as counts (%) unless otherwise stated. Baseline characteristics are reported for the 80 patients at initial visit (n= 61 males, n=19 females). Treatment details are reported for the number of patients in parentheses.

AC, adenocarcinoma; SCC, squamous cell carcinoma

Table 2 Patient-Generated Subjective Global Assessment total scores and categories ¹

	Baseline (n= 80)	3 month (n= 68)	12 month (n= 57)
PG-SGA total score	9 (0-28)	6 (2-26)	7 (0-19)
PG-SGA category scores			
A: Well-nourished	31 (38.8)	26 (38.2)	23 (40.4)
B: Moderately/suspected malnourished	47 (58.7)	40 (58.8)	32 (56.1)
C: Severely malnourished	2 (2.5)	2 (3)	2 (3.5)
Total: B + C	49 (61.2)	42 (61.8)	34 (59.6)

¹ PG-SGA total score is expressed as median (min-max). PG-SGA category scores are expressed as counts (%). PG-SGA, Patient Generated Subjective Global Assessment.

Table 3 Association between the presence of gastrointestinal symptoms (mild, moderate or severe) and Patient-Generated Subjective Global Assessment category

	Baseline n= 80 PG-SGA, n (%)			3 m n= 68 PG-SGA, n (%)			12 m n= 57 PG-SGA, n (%)		
	A	B+C	p-value	A	B+C	p-value	A	B+C	p-value
Dysphagia to solids	11 (23.4)	36 (76.6)	0.001 **	6 (24)	19 (76)	0.055	7 (33.3)	14 (66.7)	0.294
Dysphagia to fluids	5 (19.2)	21 (80.8)	0.011 *	4 (25)	12 (75)	0.171	3 (27.3)	8 (72.7)	0.264
Odynophagia to solids	9 (26.5)	25 (73.5)	0.030 *	4 (26.7)	11 (73.3)	0.231	2 (22.2)	7 (77.8)	0.204
Odynophagia to fluids	3 (15)	17 (85)	0.009 **	1 (16.7)	5 (83.3)	0.240	0 (0)	4 (100)	0.117
Regurgitation of solids	9 (27.3)	24 (72.7)	0.062	3 (20)	12 (80)	0.087	6 (37.5)	10 (62.5)	0.514
Regurgitation of fluids	7 (25.9)	20 (74.1)	0.074	2 (18.2)	9 (81.8)	0.122	6 (37.5)	10 (62.5)	0.514
Heartburn	12 (42.9)	16 (57.1)	0.401	6 (35.3)	11 (64.7)	0.482	5 (33.3)	10 (66.7)	0.346
Acid reflux	12 (34.3)	23 (65.7)	0.312	7 (30.4)	16 (69.6)	0.249	10 (41.7)	14 (58.3)	0.539
Belching	15 (30)	35 (70)	0.033 *	17 (47.2)	19 (52.8)	0.085	13 (35.1)	24 (64.9)	0.209
Nausea	3 (12)	22 (88)	0.001 **	14 (37.8)	23 (62.2)	0.569	8 (36.4)	14 (63.6)	0.419
Early satiety	7 (18.4)	31 (81.6)	0.000 ***	8 (21.1)	30 (78.9)	0.001 **	7 (28)	18 (72)	0.079
Bloating	8 (34.8)	15 (65.2)	0.420	5 (29.4)	12 (70.6)	0.285	9 (47.4)	10 (52.6)	0.315
Abdominal grumbling	10 (27)	27 (73)	0.038 *	16 (42.1)	22 (57.9)	0.314	14 (37.8)	23 (62.2)	0.402
Abdominal pain	13 (37.1)	22 (62.9)	0.489	7 (30.4)	16 (69.6)	0.249	12 (35.3)	22 (64.7)	0.251
Flatulence	16 (33.3)	32 (66.7)	0.163	17 (38.6)	27 (61.4)	0.569	14 (35)	26 (65)	0.166
Loose stools	10 (43.5)	13 (56.5)	0.380	12 (41.4)	17 (58.6)	0.449	10 (30.3)	23 (69.7)	0.062
Diarrhoea	3 (20)	12 (80)	0.084	9 (32.1)	19 (67.9)	0.271	8 (30.8)	18 (69.2)	0.140
Faecal urgency	10 (43.5)	13 (56.5)	0.380	10 (41.7)	14 (58.3)	0.431	8 (29.6)	19 (70.4)	0.097
Faecal incontinence	3 (27.3)	8 (72.7)	0.299	5 (45.5)	6 (54.5)	0.414	5 (33.3)	10 (66.7)	0.669
Hard stools	8 (22.9)	27 (77.1)	0.007 **	10 (33.3)	20 (66.7)	0.314	7 (31.8)	15 (68.2)	0.223
Constipation	6 (16.7)	30 (83.3)	0.000 ***	8 (25)	24 (75)	0.030 *	10 (43.5)	13 (56.5)	0.451
Incomplete evacuation	8 (25)	24 (75)	0.033 *	6 (21.4)	22 (78.6)	0.015 *	10 (38.5)	16 (61.5)	0.503

3 m: 3 month; 12 m: 12 month. Pearson chi-square tests were undertaken to determine the association between individuals with/without a symptom and PG-SGA category A or category B+C. Fisher's Exact tests were performed where expected cell count was less than 5. Data presented are for the association of the presence of a symptom and SGA B+C, where * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Data were incomplete as follows: Baseline; $n = 79$ for odynophagia to fluids, heartburn, faecal incontinence, hard stool; $n = 78$ for regurgitation of solids, loose stool; $n = 76$ for flatulence; $n = 72$ for constipation. 3-m; $n = 67$ for odynophagia to fluids, heartburn, loose stool. 12-m; $n = 56$ for heartburn.

Supplementary Table A Patient-Generated Subjective Global Assessment total score components¹

	Baseline (n= 80)	3 month (n= 68)	12 month (n= 57)
PG-SGA total score components			
Box 1: Weight			
0 (not changed/increased)	34 (42.5)	39 (57.3)	42 (73.7)
1 (lost in past 2 weeks)	15 (18.7)	7 (10.3)	5 (8.8)
2	10 (12.5)	6 (8.8)	3 (5.3)
3	12 (15)	8 (11.8)	4 (7)
4	6 (7.5)	7 (10.3)	3 (5.2)
5	3 (3.8)	1 (1.5)	0 (0)
<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;"> <div style="font-size: 3em; line-height: 1;">}</div> <div style="display: flex; flex-direction: column; justify-content: space-between; padding: 0 5px;"> <div>2</div> <div>3</div> <div>4</div> <div>5</div> </div> </div> <div> <p>The higher the % lost in 1- or 6 m, the higher the score. Add 1 if some lost in past 2 weeks</p> </div> </div>			
Box 2: Food intake			
0 (same/more than usual)	31 (38.8)	35 (51.5)	27 (47.4)
1 (less food than usual)	29 (36.2)	20 (29.4)	24 (42.1)
2 (little solid food)	11 (13.7)	11 (16.1)	6 (10.5)
3 (supplements only)	9 (11.3)	1 (1.5)	0 (0)
4 (very little of anything)	0 (0)	1 (1.5)	0 (0)
Box 3: Symptoms			
0-3 (none/few symptoms)	43 (53.7)	45 (66.2)	35 (61.4)
4-6 (several symptoms)	11 (13.8)	13 (19.1)	10 (17.5)
7+ (many symptoms)	26 (32.5)	10 (14.7)	12 (21.1)
Box 4: Activities and function			
0 (no limitations)	53 (66.2)	22 (32.4)	31 (54.4)
1 (not normal self)	18 (22.5)	26 (38.2)	15 (26.4)
2 (not up to most things)	7 (8.8)	11 (16.2)	7 (12.2)
3 (able for little activity)	2 (2.5)	9 (13.2)	4 (7)
Sum of Boxes 1-4			
0-6	37 (46.3)	44 (64.7)	38 (66.7)
7-12	28 (35)	14 (20.6)	14 (24.5)
13-18	10 (12.4)	9 (13.2)	5 (8.8)
19-24	5 (6.3)	1 (1.5)	0 (0)
Worksheet 2: Relevant diagnoses			
0 (no diagnoses)	2 (2.5)	0 (0)	3 (5.3)
1 (one diagnosis)	32 (40)	26 (38.2)	25 (43.9)
2 (two diagnoses)	46 (57.5)	41 (60.3)	28 (49.1)
3 (three diagnoses)	0 (0)	1 (1.5)	1 (1.7)
Worksheet 3: Metabolic demand			
0 (no demand)	80 (100)	67 (98.5)	57 (100)
1 (mild demand)	0 (0)	1 (1.5)	0 (0)

	Baseline (n= 80)	3 month (n= 68)	12 month (n= 57)
Worksheet 4: Physical examination			
0 (no deficit)	53 (66.2)	47 (69.1)	40 (70.2)
1 (mild deficit)	19 (23.8)	15 (22.1)	11 (19.3)
2 (moderate deficit)	8 (10)	6 (8.8)	5 (8.8)
3 (severe deficit)	0 (0)	0 (0)	1 (1.7)

¹ All values are expressed as counts (%)

Supplementary Table B Comparison of daily intake of energy, fibre, nutrients and food groups from food¹

	Baseline	3 m
Energy, kcal/d	2253.1 (1179.5)	2222.1 (957.4)
Protein, g/d	94.5 (46.1)	90.3 (42.8)
Carbohydrate, g/d	273.8 (157.7)	261.0 (110.4)
Alcohol, g/d	7.9 (13.3)	3.7 (6.8)
Englyst Fibre, g/d	18.9 (12.5)	17.0 (8.9)
Vitamin A, µg/d	1936.5 (1149.1)	1997.6 (1827.2)
Vitamin B ₁ , mg/d	1.7 (1.0)	1.6 (0.8)
Vitamin B ₂ , mg/d	2.5 (1.2)	2.4 (1.1)
Vitamin B ₃ , mg/d	24.4 (11.7)	23.0 (10.2)
Vitamin B ₆ , mg/d	2.5 (1.2)	2.3 (1.1)
Vitamin B ₁₂ , µg/d	9.1 (4.9)	9.2 (6.7)
Carotene, mg/d	4.3 (3.4)	4.1 (2.4)
Vitamin C, mg/d	131.1 (78.2)	130.5 (80.3)
Vitamin D, µg/d	3.7 (2.8)	3.8 (1.8)
Vitamin E, mg/d	14.3 (9.3)	13.2 (5.9)
Folate, µg/d	351.7 (178.5)	329.5 (168.5)
Calcium, mg/d	1181.1 (609.5)	1144.0 (542.1)
Chloride, mg/d	4874.0 (2720.9)	4773.8 (1649.6)
Iron, g/d	12.6 (6.5)	11.3 (4.3)
Magnesium, mg/d	362.9 (182.3)	331.3 (169.1)
Phosphorus, mg/d	1665.7 (809.1)	1598.5 (673.8)
Potassium, mg/d	4177.6 (1934.9)	3773.1 (1581.0)
Selenium, µg/d	72.3 (33.6)	69.5 (32.2)
Sodium, mg/d	3277.3 (1905.6)	3235.6 (1175.8)
Zinc, mg/d	10.8 (5.8)	10.3 (5.7)
Food groups		
Alcoholic beverages, g/d	138.9 (273.6)	70.0 (138.7)
Cereals, cereal products, g/d	270.1 (183.6)	257.9 (130.1)
Eggs, egg dishes, g/d	23.4 (25.2)	22.0 (14.8)
Fats, oils, g/d	28.0 (21.6)	30.7 (21.6)
Fish, fish products, g/d	49.2 (35.0)	46.6 (32.7)

	Baseline	3 m
Fruit, g/d	241.3 (261.9)	171.0 (184.0)
Meat, meat products, g/d	103.2 (65.4)	113.7 (82.3)
Milk, milk products, g/d	485.5 (272.7)	454.5 (206.3)
Non-alcoholic beverages, g/d	1032.5 (532.5)	932.4 (471.1)
Nuts, seeds, g/d	3.9 (6.4)	4.9 (8.3)
Potatoes, g/d	100.2 (61.5)	89.1 (50.2)
Soups, sauces, g/d	130.9 (157.1)	109.0 (93.9)
Sugars: preserves/snacks, g/d	63.5 (55.4)	64.2 (60.0)
Vegetables, g/d	319.9 (257.9)	284.0 (175.6)

3 m: 3 month; 12 m: 12 month. ¹ For all variables, results are expressed as average value/day. Results presented are available at all 3 study visits. Vitamin A refers to retinol equivalents; carotene refers to total carotene equivalents. Mauchly's Test of Sphericity was performed and Greenhouse-Geisser corrections were made if the data violated sphericity. Nutrient/food groups with significantly different means across the three time points using ANOVA (alcohol, alcohol, alcohol) Bonferroni post-hoc test was performed to determine differences between two time points, however, none were significant.

Supplementary Figure: Participant Flow Chart



